I. Disposition Of Claims

A clean version of the entire set of pending claims is attached as a separate set of pages and entitled **CLEAN VERSION OF THE ENTIRE SET OF PENDING CLAIMS**. Claims 21-30, as re-numbered by the Patent Office, are pending in the application. Reexamination and reconsideration of the application, in view of the following comments, are respectfully requested.

II. Discussion of Possession, Enablement, and Definiteness

The Patent Office rejected the claims under 35 USC 112, first paragraph, and 35 USC 112, second paragraph. The Patent Statute requires, under 35 USC 112, first paragraph, that the specification contain a written description of the invention, and of the manner and process of making and using it, in such terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and, under 35 USC 112, second paragraph, that the specification shall conclude with one or more claims particularly pointing out and distinctly claiming the invention. The Patent Office takes the position that the possession issue is governed by *University of California v. Eli Lilly*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).[1] *Accord*, MPEP § 2163 at page 2100-162, col. 1 ("A definition by function alone 'does not suffice' to sufficiently describe a coding sequence 'because it is only an indication of what the gene does, rather than what it is.").[2] The Patent Office also takes the position that the enablement issue is governed by *Ex parte Balzarini*, 21 USPQ2d 1892, 1894 (BPAI 1991) (Claims directed to medicinal treatments of diseases in highly unpredictable art areas are properly rejected under 35 USC § 112, first paragraph as lacking adequate enablement, in the absence of sufficient test data in support of the efficacy of the alleged treatment).[3] *Accord*, MPEP § 2107.03 at page

[1] Attachment 1.
[2] Attachment 2.
[3] Attachment 3.

2100-44, col. 2.[4] As for the definiteness issue, it is governed by MPEP § 2173.05(r), which states that some applications are filed with an omnibus claim that reads as follows: "A device substantially as shown and described."[5] An omnibus claim should be rejected under 35 USC 112, second paragraph, because it fails to particularly point out and distinctly claim the invention.

As stated by the Patent Office, the enablement issue is governed by *Ex parte Balzarini*, 21 USPQ2d 1892, 1894 (BPAI 1991) (Claims directed to medicinal treatments of diseases in highly unpredictable art areas are properly rejected under 35 USC § 112, first paragraph as lacking adequate enablement, in the absence of sufficient test data in support of the efficacy of the alleged treatment). *Accord*, MPEP § 2107.03 at page 2100-44, col. 2. The present case follows *Ex parte Balzarini*, because in *Ex parte Balzarini*, the evidence of record is a Declaration by Dr. Hirsch that only concludes that the test methods used in the patent specification "may" establish the compounds have utility in humans, and any conclusion as to whether a specific anti-viral compound "will" in fact be effective *in vivo* is not agreed to be predictive from the *in vitro* tests. The Declaration under 37 CFR 1.132 of Dr. Jorge R. Vila is directed to these issues (attached herewith and having Dr. Vila's Curriculum Vitae attached as Exhibit 1).* It states that the test methods using *quiescent* human peripheral blood lymphocyte (PBL) cells as outlined in Malley et al., Proc. Natl. Acad. Sci. USA 91:11017 (1994)[6] (identifying synergistic effect of hydroxyurea and 2', 3'-dideoxyinosine (ddI)), of which he is the last-named author, are accepted by those skilled in the anti-human immunodeficiency virus (HIV) art as providing a reasonable basis for a conclusion that the active agent under investigation will have utility for inhibiting replication of the virus in human cells *in vivo*, because the combination of hydroxyurea and ddI is effective *in*

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[4] Attachment 4.
[5] Attachment 5.
* See Declaration under 37 CRF 1.132 of Nancy W. Venkso explaining that Dr. Vila has a financial interest in the above-identified application.
[6] Attachment 6.

vivo and predictive from the *in vitro* tests using quiescent human PBL cells, as demonstrated by human clinical trials, per Vila et al., Lancet 350:635 (1997),[7] of which he is the first-named author. Additionally, the Declaration of Dr. Vila states that the test methods using *activated* human PBL cells as outlined in Gao et al., Proc. Natl. Acad. Sci. USA 90:8925 (1993)[8] and Lori et al., Science 266:801 (1994)[9] (identifying synergistic effect of hydroxyurea and ddI) are also accepted by those skilled in the anti-HIV art as providing a reasonable basis for a conclusion that the active agent under investigation will have utility for inhibiting replication of the virus in human cells *in vivo*, because the combination of hydroxyurea and ddI is effective *in vivo* and predictive from the *in vitro* tests using activated human PBL cells, as demonstrated by human clinical trials, per Vila et al., above. The Declaration of Dr. Vila concludes that, although the test methods using quiescent human PBL cells may provide a *better* basis for a conclusion that the active agent under investigation will have utility for inhibiting replication of the virus in human cells *in vivo* (because viral DNA synthesis is known to take place in quiescent cells), the test methods using activated human PBL cells provide a *reasonable* basis for this conclusion (because a conclusion as to whether the combination would be effective *in vivo* was predictive from the *in vitro* tests), and that a conclusion as to whether a specific anti-viral compound will in fact be effective *in vivo* is reasonably predictive from the *in vitro* tests using activated human PBL cells. As agreed by *Ex parte Balzarini*, claims directed to medicinal treatments of diseases in highly unpredictable art areas meet the requirements of 35 USC § 112, first paragraph for providing amble enablement, in the presence of sufficient test data in support of the efficacy of the alleged treatment, where, as here, the test data is reasonably predictive (even if not perfect, i.e., by virtue of identifying AZT). Under *Ex parte Balzarini*, the claims meet the enablement requirement.

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[7] Attachment 7.
[8] Attachment 8.
[9] Attachment 9.

As stated by the Patent Office, the possession issue is governed by *University of California v. Eli Lilly*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). *Accord*, MPEP § 2163 at page 2100-162, col. 1 ("A definition by function alone 'does not suffice' to sufficiently describe a coding sequence 'because it is only an indication of what the gene does, rather than what it is."). MPEP § 2163 at page 2100-164, paragraph bridging col. 1 and col. 2 does not say, however, that the written description requirement for a claimed genus may never be satisfied. Rather, it says that the written description requirement for a claimed genus may indeed be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. The Declaration of Dr. Vila is directed to these issues. It states that, in view of the combination of hydroxyurea, a ribonucleotide reductase inhibitor, and ddI, a nucleoside reverse transcriptase inhibitor (NRTI), it is obvious that this principle should be viable for the combination of other NRTIs, and that any modality that would deplete the intracellular pool of deoxyribonucleotide phosphates could substitute for hydroxyurea. *Accord,* J. Balzarini, Pharmacology & Therapeutics 87: 175-187 (2000) at page 176, col. 2, last line before section 2, and page 179, col. 2, first line of new paragraph.[10] *See also,* Malley et al., Lancet 343:1292 (1994) (substitution of DAH, another ribonucleotide reductase inhibitor, for hydroxyurea)[11] and Gao et al., Biochem Pharmacol 50:274 (1995) (substitution of 2'-F-dd-ara-A, another antiviral nucleoside phosphate analog, for ddI).[12] The claims cover use of a synergistic combination of an inhibitor of ribonucleotide reductase and an antiviral nucleoside phosphate analog other

[10] Attachment 10.
[11] Attachment 11.
[12] Attachment 12.

than a thymidine or cytidine analog. The phrases "an inhibitor of ribonucleotide reductase" and "an antiviral nucleoside phosphate analog" are as accurate as the subject matter permits, such components of a mixture being undefinable by "chicken wire" structural formulas known to organic chemists. As agreed by the MPEP, where, as here, a definition is by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, the written description requirement for a claimed genus is satisfied.

As stated above, the definiteness issue is governed by MPEP § 2173.05(r). Due to the fact that no claim reads "A device substantially as shown and described," none of the claims is an omnibus claim. Consequently, the claims should not be rejected under 35 USC 112, second paragraph.

III. Discussion of Double Patenting

The Patent Office rejected the claims on the grounds of obviousness-type double patenting over claims 1-3 of USP 5,521,161, claims 1-3 of USP 5,736,527, claims 12-22 of USP 6,046,175, claims 6-8 of USP 6,093,702, and claims 3-8 of USP 6,194,390. A terminal disclaimer may be used to overcome an obviousness-type double patenting rejection. Applicant will defer filing a terminal disclaimer until the rejected claims are otherwise indicated to be in condition for allowance.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4/2/03

By: _____

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CLEAN VERSION OF ENTIRE SET OF PENDING CLAIMS

21. A method for inhibiting replication of reverse transcriptase dependent virus in animal cells, comprising the step of administering to said cells a synergistic combination of an inhibitor of ribonucleotide reductase and an antiviral nucleoside phosphate analog other than a thymidine or cytidine analog.
22. The method of claim 21, wherein said virus is a retrovirus.
23. The method of claim 21, wherein said virus is the human immunodeficiency virus (HIV).
24. The method of claim 21, wherein said inhibitor of ribonucleotide reductase is hydroxyurea.
25. The method of claim 21, wherein said antiviral nucleoside phosphate analog is an agent that serves to inhibit replication of said virus by terminating DNA chain elongation.
26. The method of claim 25, wherein said agent that serves to inhibit replication of said virus by terminating DNA chain elongation inhibits replication by premature termination of viral DNA synthesis to produce incomplete viral DNA.
27. The method of claims 25, wherein said agent is a dideoxynucleoside.
28. The method of claims 27, wherein said dideoxynucleoside is 2',3'-dideoxyinosine (ddI).
29. The method of claim 27, wherein said dideoxynucleoside is a 2'-fluoro purine dideoxynucleoside.
30. The method of claim 29, wherein said 2'-fluoro purine dideoxynucleoside is one of the following compounds: 2'-fluoro-2',3'-dideoxyadenosine (2'-F-dd-ara-A), 2'-fluoro-2',3'-dideoxyinosine (2'-F-dd-ara-I), or 2'-fluoro-2',3'-dideoxyguanosine (2'-F-dd-ara-G).